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An Open-label, Multicenter Study of Flecainide Acetate Oral Inhalation Solution for Acute Conversion of Recent-onset, Symptomatic Atrial Fibrillation to Sinus Rhythm

Crijns: Oral inhaled flecainide converts AF to SR

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Abstract

Background: Oral and intravenous (IV) flecainide is recommended for cardioversion of atrial fibrillation (AF). In this open-label, dose-escalation study, the feasibility of delivering flecainide via oral inhalation (flecainide acetate inhalation solution [FlecIH]) for acute conversion was evaluated. We hypothesized that flecainide delivered by oral inhalation would quickly reach plasma concentrations sufficient to restore sinus rhythm (SR) in patients with recent-onset AF.

Methods: Patients (n=101) with symptomatic AF (for ≤ 48 hours) self administered FlecIH using a nebulizer (30 mg [n=10], 60 mg [n=22], 90 mg [n=21], 120 mg [n=19], and 120 mg in a formulation containing saccharin [n=29]). Electrocardiograms and flecainide plasma concentrations were obtained, cardiac rhythm using 4-hour Holter was monitored, and adverse events (AEs) were recorded.

Results: Conversion rates increased with dose and with the maximum plasma concentrations (C_{max}) of flecainide. At highest dose, 48% of patients converted to SR within 90 minutes from start of inhalation. Among patients who achieved a Cmax > 200 ng/mL, the conversion rate within 90 minutes was 50%; for those who achieved a Cmax< 200 ng/mL, it was 24%. Conversion was rapid (median time to conversion of 8.1 minutes from end of inhalation), and conversion led to symptom resolution in 86% of the responders. AEs were typically mild and transient, and included: cough, throat pain, throat irritation; at highest dose with the formulation containing saccharin, these AEs were reported by 41%, 14%, and 3% of patients, respectively. Cardiac AEs consistent with those observed with oral and IV flecainide were uncommon and included post-conversion pauses (n=2), bradycardia (n=1), and atrial flutter with 1:1 atrioventricular conduction (n=1); none required treatment, and all resolved without sequelae.

Conclusions: Administration of flecainide via oral inhalation was shown to be safe and to yield plasma concentrations of flecainide sufficient to restore SR in patients with recent-onset AF.

Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT03539302

Non-standard Abbreviations and Acronyms

AE – adverse event
AESI – adverse event of special interest
AF - atrial fibrillation
BP – blood pressure
C_{max} - maximum plasma concentration
ECG – electrocardiogram
eTLD - estimated total lung dose
FlecIH - flecainide acetate inhalation solution
IV – intravenous
LV – left ventricular
SR – sinus rhythm

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice. Both the incidence and prevalence of AF increase exponentially with age with an estimated 10% prevalence in patients > 80 years of age. For the prompt restoration of sinus rhythm (SR) in symptomatic patients with AF pharmacological cardioversion is considered an appropriate strategy.[1] Currently available oral and intravenous (IV) antiarrhythmic agents for acute conversion of recent-onset AF to SR have limitations. For oral dosing, cardioversion can take hours, and for IV dosing, in-hospital administration is required and long periods of monitoring may be necessary (eg, ibutilide[2]).

Flecainide is a potent cardiac sodium channel blocker and recommended for pharmacological cardioversion of recent-onset AF in patients without known relevant structural heart disease.[1] The conversion rate of AF to SR following IV flecainide has been reported to be in the range of 51-55% within 2-3 hours of dosing.[1, 3]

An inhaled version of flecainide acetate is being developed for the acute conversion of recent-onset AF to SR in symptomatic patients without contraindications to the drug. The oral inhalation route of administration offers a more convenient dosage form that delivers a rapid bolus of flecainide into the systemic circulation to yield plasma concentrations that may be sufficient to convert AF to SR.[4, 5] In the present study we evaluated the feasibility, tolerability and preliminary efficacy of inhalation solutions of flecainide acetate at estimated total lung doses (eTLD) of 30 mg, 60 mg, and 90 mg, and 120 mg in patients with recent-onset AF.

Methods

Study Design

This was an open-label, multicenter study designed to evaluate inhaled flecainide (FlecIH) for acute conversion of recent-onset AF to SR. Initially, patients were randomized 1:1 to a 30 mg or 60 mg dose regimen. Based on safety, tolerability, and efficacy data from the 30 mg and 60 mg dose groups, the study was expanded to an open-label non-randomized, ascending dose study that continued with additional patients in the 60 mg dose group before adding dose regimens of 90 mg and 120 mg (using two formulations). All doses described were estimated total lung doses (eTLDs).

The study was conducted at 15 centers in Belgium and the Netherlands. The protocol was approved by the independent ethics committee at each participating site. An independent data and safety monitoring board reviewed pertinent data to ensure the safety of the patients participating in the study. All patients provided written informed consent before any protocol-specific screening procedures or any study drugs were administered.

The data that support the findings of this study are available from the corresponding authors)upon reasonable request.

Participants

Adult patients presenting to the Emergency Department were eligible for the study if they had recent-onset (≤ 48 hours) symptomatic AF that was categorized as either a first diagnosed episode, a recurrent paroxysmal episode, or an episode post-cardiac ablation for paroxysmal AF. Patients were to have no contraindications to flecainide, such as heart failure, myocardial ischemia, or structural heart disease.

Treatments

Four eTLDs were evaluated: a 30 mg dose administered as a single inhalation period over 4.5 minutes; a 60 mg dose and a 90 mg dose, administered as 2 inhalation periods of 4.5 minutes each (2 × 30 mg and 2 × 45 mg, respectively), separated by a 1-minute break; and a 120 mg dose administered as 2 inhalation periods of 3.5 minutes each (2 × 60 mg), separated by a 1-minute break. The 30, 60, and 90 mg doses utilized a formulation containing a flecainide acetate concentration of 35 or 45 mg/mL (FlecIH-101), and the doses were administered to completion of the full inhalation duration. For the 120 mg dose, two formulations (FlecIH-102 and FlecIH-103) were evaluated, both contained a flecainide acetate concentration of 75 mg/mL with saccharin added to FlecIH-103 to improve the organoleptic properties of the inhalation solution. The 120 mg doses were inhaled until conversion to SR or until the full inhalation was completed, whichever occurred first.

FlecIH was delivered via the AeroEclipse II BAN inhalation system (Trudell Medical, Canada), a hand-held, breath actuated nebulizer, operated through compressed air at a flow rate of 5 or 8 L/minutes.

Outcomes

The primary outcomes were the feasibility (i.e., patients completed the planned inhalations, drug was administered and ECGs were recorded in a seated position) and tolerability of administering flecainide acetate via oral inhalation for acute conversion of symptomatic recent onset AF to SR. The primary outcome was supported by the observed efficacy (conversion rates), safety, pharmacokinetics (C_{max}), and pharmacodynamics (ECG intervals). Efficacy outcomes included the proportion of patients whose AF converted to SR within 60 and 90 minutes after initiation of inhalation, which was evaluated based on (a) dose and (b) C_{max} of

flecainide, and time to conversion. The proportion of patients with AF symptoms was assessed at intervals up to 90 minutes postdose. Safety was assessed through the patient-incidence and severity of adverse events (AEs).

Statistical Analysis

A sample size of 100 patients was planned based on clinical judgment and the objectives of the study; no formal sample size calculations were performed.

All enrolled patients who received any amount of inhaled study drug were included in the safety analyses. All enrolled patients who were in AF at the start of inhalation and who completed the assigned inhalation regimen (per the cohort) were included in the efficacy analyses. All enrolled patients who completed the assigned inhalation regimen (per the cohort) were included in the pharmacokinetic analyses.

The proportion of patients within each treatment group who converted within 60 and 90 minutes after initiation of dosing and the proportion of patients with reduced or no AF symptoms up to 90 minutes postdose were summarized. The conversion rate, irrespective of the eTLD inhaled, was also estimated based on C_{max} values > 200 ng/mL versus < 200 ng/mL, as this concentration is the lower boundary of the estimated therapeutic range of 200 to 1000 ng/mL for flecainide to suppress ventricular ectopy.[6]

Results

Disposition

From June 13, 2018 through March 6, 2020, 105 patients with recent-onset AF were enrolled in the study. Four of the enrolled patients spontaneously converted to SR during predose monitoring and did not receive study drug (Table 1).

All patients completed the first inhalation period; however, 4 patients (2 each in the 120 mg FlecIH-102 and 120 mg FlecIH-103 groups) did not initiate the planned second inhalation period due to conversion to SR (n=2) or an AE (n=2). The mean duration of study drug inhalation for each treatment group was 4.6 minutes for the 30 mg group, 9.1 minutes for both the 60 mg and 90 mg groups, and 6.5 and 6.7 minutes for the 120 mg FlecIH-102 and FlecIH-103 groups, respectively. The 1-minute break is not included in the drug inhalation duration for the regimens with 2 inhalation periods.

Baseline Characteristics

As summarized in Table 1, baseline characteristics were generally similar across treatment groups. The mean duration of the presenting AF episode ranged from 10.6 hours to 19.7 hours, the majority of patients (80.2%) showed a duration ≤ 24 hours and for 46.5% the presenting episode was their first diagnosed AF. Further details in the Supplement.

During screening, all patients had at least 1 symptom associated with AF, which included: palpitations (70%–90% across groups), lightheadedness or dizziness (35%–50%), shortness of breath (24%–44%), and chest discomfort (29%–60%).

Conversion of AF to SR

A total of 33 patients across all treatment groups had their AF converted to SR within 60 minutes after initiation of FlecIH. Conversion rates were 10% in the 30 mg group, 35.0% in the 60 mg group, 33.3% in the 90 mg group, and 35.3% and 44.4% in the 120 mg FlecIH-102 and 120 mg FlecIH-103 groups, respectively. By 90 minutes after the start of dosing, 2 additional patients, 1 each in the 120 mg FlecIH-102 and 120 mg FlecIH-103 groups, converted to SR; the increased conversion rates in these 2 groups were 41.2% and 48.1%, respectively.

Among the 33 patients whose AF converted to SR within 60 minutes after the start of dosing, half of the conversions occurred within 20 minutes of initiation of dosing (Figure 1), including 6 patients whose AF converted to SR before FlecIH dosing had completed. The median time to conversion was 3.9 minutes (range: −6.6 to 39 minutes, IQR = 17 minutes) from the end of dosing and 14.3 minutes (range: 2.0 to 47 minutes, IQR = 16 minutes) from the start of dosing. Among the 35 patients whose AF converted to SR within 90 minutes, the median time to conversion was 8.1 minutes (range: −6.6 to 74 minutes, IQR = 19 minutes) from the end of dosing and 16.6 minutes (range: 2.0 to 82 minutes, IQR = 19 minutes) from the start of dosing. The effects of conversion on symptoms are shown in Figure 2 and in the Supplement. There were no recurrences prior to discharge on Day 1.

Flecainide Plasma Concentrations Following Inhalation

Peak plasma levels (C_{max} observed) typically occurred within 3 minutes after completion of the inhalation. The corresponding C_{max} values generally increased with dose (30, 60, 90 and 120 mg [FlecIH-102] and 120 mg [FlecIH-103] eTLDs), with mean (SD) values of 127 (100), 213 (217), 262 (229), 407 (263), and 386 (209) ng/mL, respectively. The proportion of patients with C_{max} values falling within the estimated therapeutic range (200 to 1000 ng/mL) increased with dose from 10% for the 30 mg eTLD to 77% for the 120 mg the FlecIH-103 eTLD. Patients

who inhaled the 120 mg FlecIH-103 eTLD achieved a nearly optimal C_{max} profile with the majority of them having values above 200 ng/mL, and no patient having a C_{max} above 1000 ng/mL (Figure 3). As shown in Figure 3 it is evident that there was a large inter-subject variability in C_{max} values.

Conversion Rate Based on Maximum Flecainide Plasma Concentration

There were 48 patients with a C_{max} > 200 ng/mL and 46 patients with a C_{max} < 200 ng/mL. Among patients who achieved a Cmax > 200 ng/mL, the conversion rate within 90 minutes was 50%, whereas for those who achieved a Cmax< 200 ng/mL, the conversion rate was 24%. An additional analysis of conversion rate was carried out for patients given the 120 mg eTLD (FlecIH-102/FlecIH-103) using C_{max} cut-off values of < 200 ng/mL (n=11), 200 - 500 ng/mL (n=20) and > 500 ng/mL (n=13); and conversion rates based on these C_{max} cut-off values were: 18% (2/11), 50% (10/20) and 62% (8/13), respectively.

Effects of inhaled flecainide on QRS intervals are presented in Supplemental Table S1.

Adverse Events

Treatment-emergent AEs considered by the investigator as related to study drug were reported for 76% of patients across the dose groups. The patient-incidence of AEs was similar across dose groups (Table 2), but the severity of AEs generally increased with dose, with a greater proportion of patients in the 120 mg groups having a moderate or severe AE compared with the lower dose groups (data not shown). By MedDRA (version 22.0) preferred term, AEs most frequently reported (> 10%) were cough (52% of all patients), oropharyngeal pain (15%), and throat irritation (12%). As shown in Table 2, in the 120 mg eTLD cohort that received the

FlecIH-103 (solution containing saccharin), the incidence of cough, oropharyngeal pain and throat irritation were reduced to 41%, 14% and 3%, respectively.

Predefined cardiovascular AEs of special interest (AESI) were collected in the present study based on investigator-reported AEs and review of vital signs and ECGs. A total of 14 patients had at least one cardiovascular AESI, including transient hypotension (8 patients: 1 in each of the 30, 60, and 90 mg groups, 2 in the 120 mg FlecIH-102 group and 3 in the 120 mg FlecIH-103 group) and bradycardia (4 patients: 1 in each of the 30 and 90 mg groups and 2 in the 120 mg FlecIH-103 group). Serious AEs considered related to study drug occurred in 4 patients, including 2 cases of transient sinus arrest, 1 case of atrial flutter (with 1:1 conduction and rapid ventricular rate), and a case of bradycardia (11 episodes of RR interval durations longer than 2 seconds [range 2 to 3 seconds]). The vital signs changes associated with these AEs were self-limited and the majority of patients were asymptomatic; none required medication to resolve. In most cases, these AEs were resolved when the subsequent vital signs measurement was taken. For futher details see Supplement.

Discussion

In the present open-label, dose-escalation study, delivering flecainide via oral inhalation for conversion of AF to SR in patients with symptomatic episodes of ≤ 48 hours appeared feasible and was well-tolerated. Furthermore, the conversion rate within 90 minutes of the start of inhalation at the highest dose with the FlecIH-103 solution was 48% and among patients given the 120 mg eTLD in whom the C_{max} of flecainide was > 200 ng/mL, the conversion rate was 55%. Across all dose groups, restoration of SR occurred within a median of 8.1 minutes after the end of the inhalation. Therefore, the results of this study show that orally inhaled flecainide has the potential to be a safe, rapid and effective method for acute conversion of recent-onset AF to SR.

The conversion rates with orally inhaled flecainide seen in the present study are within the range reported for IV vernakalant (51.6%) and higher than reported for IV amiodarone (5%).[7] The conversion rates for other anti-arrhythmic drugs, including IV flecainide vary widely.[1, 3, 8, 9] Pharmacologic conversion rates of recent-onset AF (≥ 1 hour to ≤ 48 hours) within 90 minutes for IV flecainide or ibutilide were 56.4% and 50%, respectively.[10] In comparison, the spontaneous conversion rate within 2 hours of AF onset ranges from 5% to 16%.[11, 12] Therefore, the conversion rate in this feasibility study in patients receiving the 120 mg eTLD appears to be in the range of reported rates for IV flecainide, vernakalant and ibutilide.

The therapeutic concentration of flecainide in the systemic circulation is generally in the range of 200 to 1,000 ng/mL.[6] Consistent with that, the conversion rate of AF to SR within 90 minutes of initiation of inhalation of flecainide, irrespective of the dose, was 2-fold higher for patients whose C_{max} values were > 200 ng/mL compared with those whose C_{max} values were < 200 ng/mL. However, there were some patients in whom C_{max} values were below 200 ng/mL and

had their AF converted to SR, whereas others with plasma levels within the therapeutic range did not convert. Because of the small sample size it is premature to reach a definitive conclusion that the C_{max} threshold for conversion is > 200 ng/mL. Nonetheless, the likelihood of achieving a C_{max} > 200 ng/mL increased with dose from 30 mg to 120 mg, and importantly, at the 120 mg eTLD (FlecIH-103), 77% of patients achieved a C_{max} > 200 ng/mL (Figure 3). In addition, for the combined 120 mg patient-cohorts, there appears to be a trend toward higher conversion rates with increasing C_{max} values (eg, 62% for C_{max} values >500 ng/mL). This interpretation is not meant to imply that the plasma level of flecainide achieved is the only determinant of efficacy. In fact, plasma levels of flecainide achieved via oral inhalation, which is similar to a bolus injection as opposed to an infusion, may not be a reliable surrogate for efficacy. Furthermore, there was significant variability in C_{max} values at each dose level, which is not unexpected for flecainide considering that similar variability has been reported for IV flecainide.[13, 14]

The doses of inhaled flecainide evaluated in this study were shown to be safe; no major complication was reported. As to tolerability of the inhalation regimen, all patients completed the first inhalation period and only two did not complete the second inhalation period due to an AE. Importantly, all reported cardiovascular AEs were self-limited, hence, none required medication. The characteristics of the reported cough suggest that it was a reflex cough, stimulated by inhalation of a solution/aerosol containing an organic acid or the aerosol 'fog' acting as an irritant.[15-17] In general, the cough (without mucus or wheezing) was either a 'single cough' or repeated single coughs resembling a cough 'epoch' that disappeared or subsided within seconds as the inhalation continued. On no occasion did a patient have to discontinue the inhalation due to the cough. Nevertheless, oral inhalation of medications can be challenging for some patients due to the organoleptic properties of the inhalation solution, and training on proper inhalation

technique is important to achieve optimal results. Thus, improvements in the organoleptic properties of the inhalation solution and additional training on the inhalation could result in higher efficacy.

Conclusions

The results of this study show for the first time that it is feasible to administer flecainide via oral inhalation for conversion of recent-onset AF to SR achieving a conversion rate as high as 50% within 90 minutes of initiation of inhalation. The conversion rate was dependent on dose, inhalation solution, and C_{max} achieved. Overall, administration of flecainide via oral inhalation was safe with no major complications reported. Thus, the results of this preliminary evaluation of flecainide delivery via oral inhalation for cardioversion of symptomatic recent-onset AF suggest that oral inhaled flecainide has the potential to be a practical option for rapid conversion of AF to SR, and prompt relief of symptoms, resulting in shorter lengths of stay in an Emergency Department and thereby reduced hospital admissions. In the future, if the safety profile warrants, this method of delivery of flecainide may be developed for out-of-hospital use, akin to pill-in-the-pocket,[18] but enabling more rapid restoration of sinus rhythm.

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Preparation of study protocol and execution of study: Cardialysis (contract Research Organization, Rotterdam, Netherlands) and Clinical Operations of InCarda Therapeutics.

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Disclosures

Drs. Ruskin, Camm and Kowey have been paid consultants for InCarda Therapeutics.

P. Madhavapeddi and L. Belardinelli are employees of InCarda Therapeutics Inc. and hold stock in the company.

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Legends to Figures

Figure 1. Cumulative percentage of patients whose AF converted to SR within 90 minutes from the start of inhalation of flecainide. Total duration of inhalation period(s): 30 mg group: 4.5 min; 60 mg, and 90 mg groups: 10 min; 120 mg groups: 8 min

Figure 2. Comparison of reported AF-related symptoms up to 90 minutes from the end of inhalation of flecainide for patients whose AF converted (n=35) and did not convert (n=44) to SR (not included are data from 16 patients whose AF did not convert to SR before undergoing electrical cardioversion between 60 and 90 minutes of dosing). At baseline, all patients (n=95) had at least one of the following AF-related symptoms prior to the start of inhalation: palpitations, lightheadedness or dizziness, shortness of breath, and chest discomfort. The bars denote the percentage of patients who had no symptoms or reduced AF-related symptoms.

Figure 3. Observed peak plasma levels (C_{max} value) for individual patients at each of the estimated total lung doses (eTLDs) studied. The estimated therapeutic range for suppression of ventricular ectopy by flecainide of 200-1000 ng/mL is illustrated by the horizontal boundary lines. C_{max} values of the patients whose AF converted to SR are denoted by green dots whereas those whose AF did not convert are denoted by brown dots. The number (%) at the top and bottom of each dose cohort denote the respective number and corresponding percentage of patients whose C_{max} values were either above or below 200 ng/mL.

Figure 4. QRS interval duration (left panel) and changes (Δ) in QRS interval duration from baseline (right panel) over time following inhalation of 120 mg FlecIH-103. Data are from n = 26 patients; each data point represents the mean (± SD). EOI denotes the end of the inhalation.

Table 1. Baseline Characteristics by Treatment Group

Characteristic	Dose Regimen				
	30 mg (n=10)	**60 mg (n=22)**	**90 mg (n=21)**	**120 mg FlecIH-102 (n=19)**	**120 mg FlecIH-103 (n=29)**
Age, y, mean (SD)	59.3 (6.5)	62.0 (13.4)	58.9 (9.3)	63.4 (8.6)	62.6 (12.4)
Male sex, n (%)	9 (90.0)	17 (77.3)	14 (66.7)	8 (42.1)	19 (65.5)
White race, n (%)	8 (80.0)	21 (95.5%)	18 (85.7%)	18 (94.7%)	26 (89.7%)
Body mass index (kg/m^2), mean (SD)	26.9 (3.9)	26.3 (3.1)	27.3 (3.9)	28.2 (5.4)	26.7 (3.7)
Risk Factors					
Hypertension, n (%)*	5 (50.0%)	12 (54.5%)	7 (33.3%)	10 (52.6%)	9 (31.0%)
Hyperlipidemia, n (%)	2 (20.0%)	8 (36.4%)	7 (33.3%)	8 (42.1%)	9 (31.0%)
Diabetes, n (%)	0	2 (9.1%)	3 (14.3%)	1 (5.3%)	1 (3.4%)
Heart failure, n (%)	1 (10.0%)	0	1 (4.8%)	0	3 (10.3%)
CHA_2DS_2-VASc score, mean (SD)†	1.1 (0.9)	1.6 (1.5)	1.3 (1.3)	1.7 (1.4)	1.6 (1.5)
AF at Presentation					
Duration, h, mean (SD)	19.7 (14.1)	18.5 (12.8)	15.6 (10.4)	10.6 (6.7)	13.2 (10.3)
≥ 1 h up to ≤ 24 h, n (%)	6 (60.0%)	14 (63.6%)	18 (85.7%)	18 (94.7%)	25 (86.2%)

Characteristic	Dose Regimen				
	30 mg (n=10)	**60 mg (n=22)**	**90 mg (n=21)**	**120 mg FlecIH-102 (n=19)**	**120 mg FlecIH-103 (n=29)**
> 24 h up to ≤ 48 h, n (%)	4 (40.0%)	8 (36.4%)	3 (14.3%)	1 (5.3%)	4 (13.8%)
Newly diagnosed, n (%)	6 (60.0%)	11 (50.0%)	8 (38.1%)	9 (47.4%)	13 (44.8%)
Recurrent, n (%)	4 (40.0%)	10 (45.5%)	10 (47.6%)	9 (47.4%)	15 (51.7%)
Post-ablation, n (%)	0	1 (4.5%)	3 (14.3%)	1 (5.3%)	1 (3.4%)

* Resting BP > 140/90 mmHg on at least 2 occasions or currently receiving antihypertensive pharmacologic treatment

† Scores can range from 0 to 9; the higher the score, the greater the risk for stroke.

Table 2. Summary of Adverse Events Considered Related to Study Drug (Reported for ≥ 5% of Patients)

	Dose Regimen				
	30 mg (n=10)	**60 mg (n=22)**	**90 mg (n=21)**	**120 mg FlecIH-102 (n=19)**	**120 mg FlecIH-103 (n=29)**
Cough	8 (80)	9 (41)	11 (52)	13 (68)	12 (41)
Oropharyngeal pain	0	3 (14)	4 (19)	4 (21)	4 (14)
Throat irritation	1 (10)	6 (27)	1 (5)	3 (16)	1 (3)
Dysphagia	0	2 (9)	3 (14)	2 (11)	2 (7)
Dyspnea	0	0	1 (5)	3 (16)	3 (10)
Hypotension	1 (10)	1 (5)	1 (5)	1 (5)	3 (10)
Salivary hypersecretion	0	1 (5)	4 (19)	1 (5)	1 (3)

30 mg eTLD, n=10
60 mg eTLD, n=20
90 mg eTLD, n=21
120 mg eTLD (FlecIH-102), n=17
120 mg eTLD (FlecIH-103), n=27

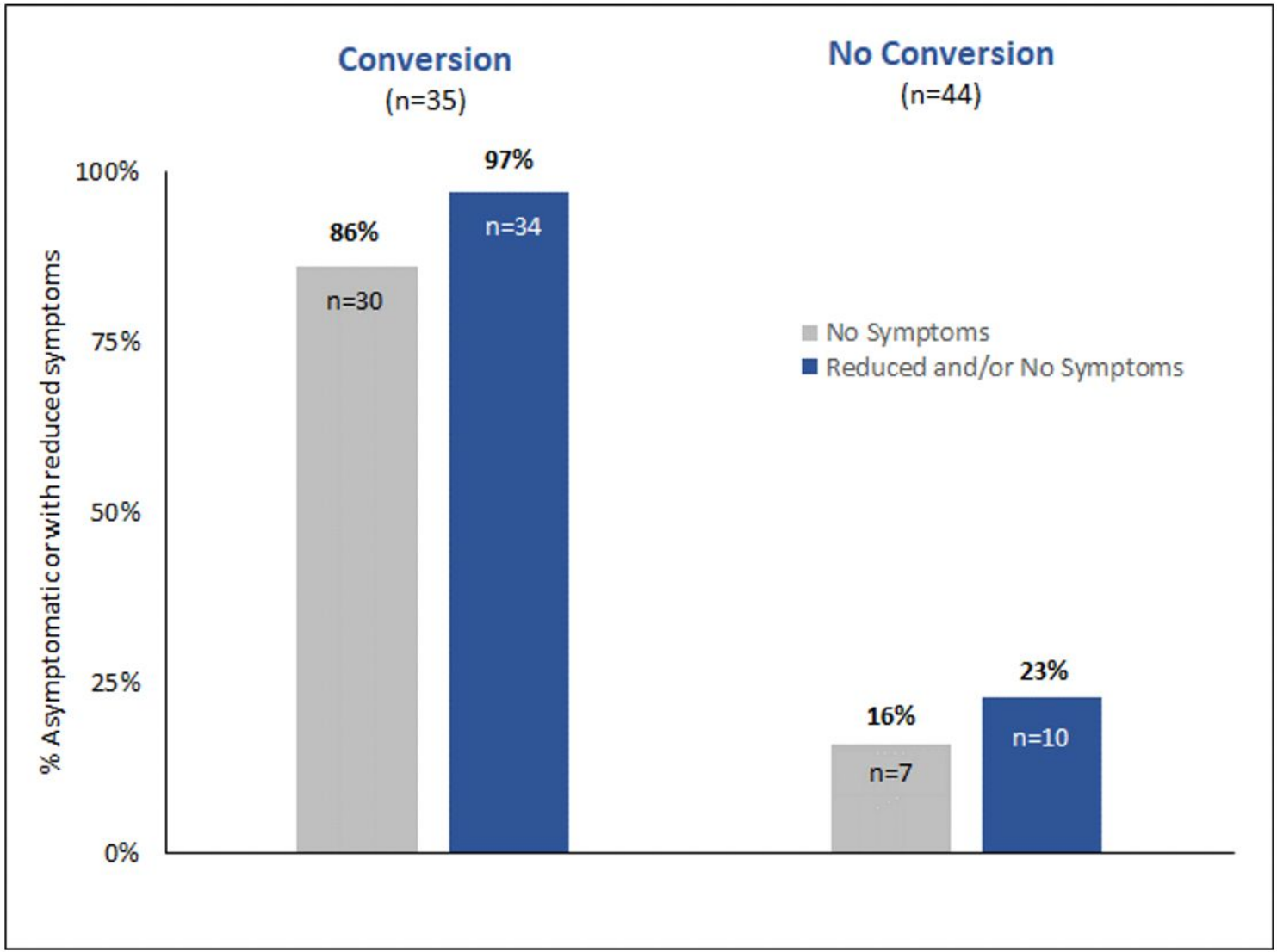
(48%)
(41%)
(35%)
(32%)
(10%)

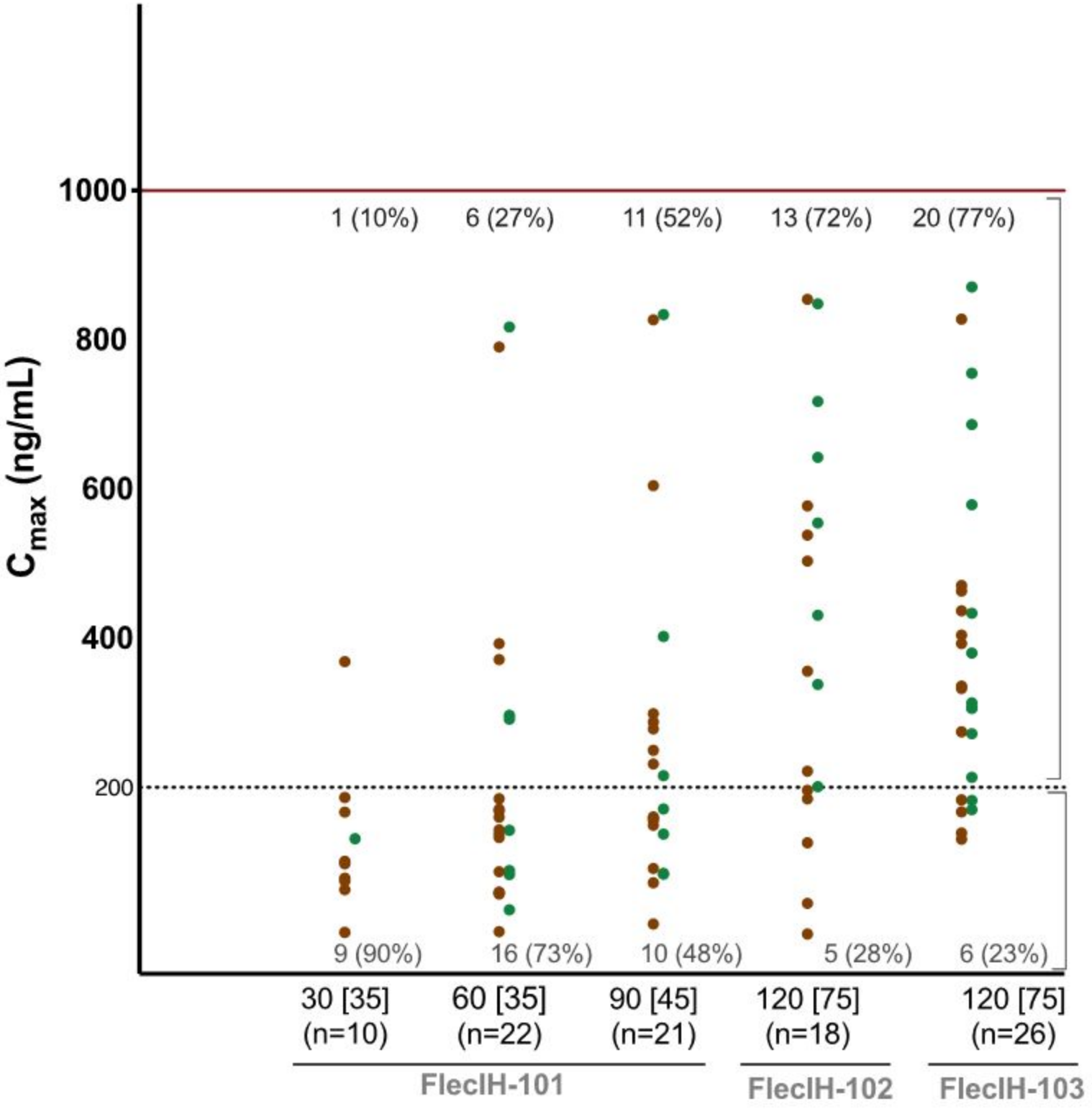
Percentage of patients whose AF converted to SR

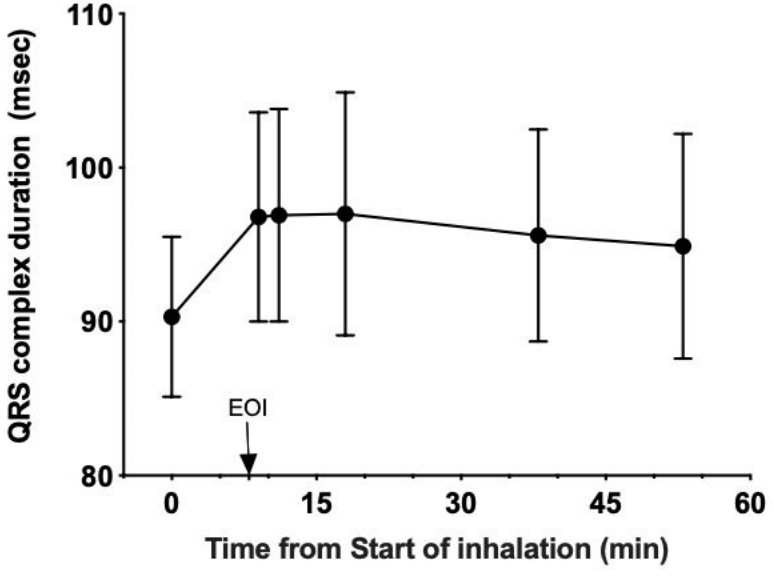
60
50
40
30
20
10
0

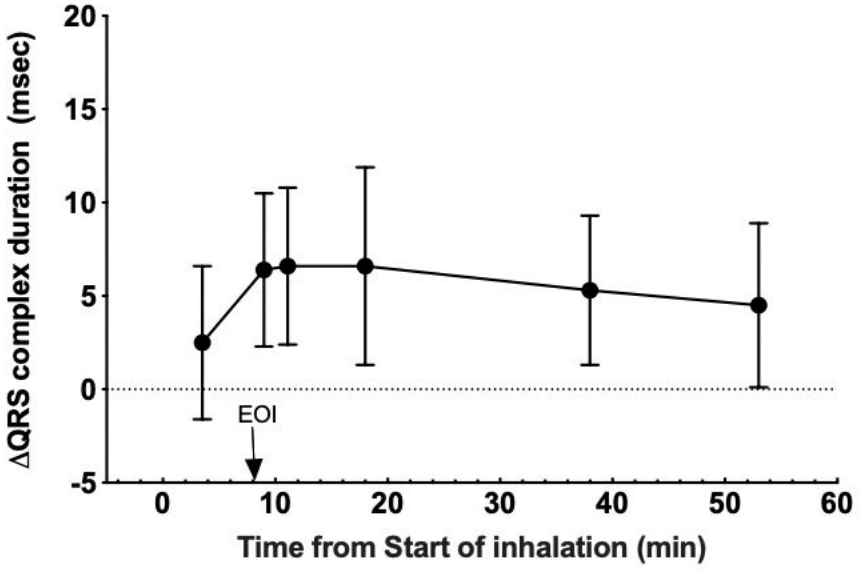
0
20
40
60
80
100

Time to Conversion of AF to SR (minutes)


Conversion
(n=35)
No Conversion
(n=44)
100%
75%
50%
25%
0%
% Asymptomatic or with reduced symptoms
86%
n=30
97%
n=34
16%
n=7
23%
n=10
No Symptoms
Reduced and/or No Symptoms


1000
800
600
400
200
C_{max} (ng/mL)
1 (10%)
6 (27%)
11 (52%)
13 (72%)
20 (77%)
9 (90%)
16 (73%)
10 (48%)
5 (28%)
6 (23%)
30 [35] (n=10)
60 [35] (n=22)
90 [45] (n=21)
120 [75] (n=18)
120 [75] (n=26)
FlecIH-101
FlecIH-102
FlecIH-103
eTLD mg [Conc of flecainide in IH solution]


QRS complex duration (msec)
110
100
90
80
EOI
0
15
30
45
60
Time from Start of inhalation (min)


ΔQRS complex duration (msec)
20
15
10
5
0
-5
EOI
0
10
20
30
40
50
60
Time from Start of inhalation (min)